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L17: Entry 16 of 22 File: USPT Nov 25, 1997

DOCUMENT-IDENTIFIER: US 5690926 A
TITLE: Pluripotential embryonic cells and methods of making same

Brief Summary Text (6):
Previous studies have shown that steel factor (SF) and leukemia inhibitory factor (LIF) synergistically promote the survival and in some eases the proliferation of mouse PGCs in culture (Godin et al., 1991; Dolci et al., 1991; Matsui et al., 1991). However, under these conditions, PGCs have a finite proliferative capacity that correlates with their cessation of division in vivo. A similar finite proliferative capacity has been reported for oligodendrocyte-type 2 astrocyte (O-2A) progenitor cells in the rat optic nerve. In this case, PDGF is involved in the self renewal growth of O-2A cells (Noble et al., 1988; Raft et al., 1988). After a determined number of cell divisions, O-2A cells may lose their responsiveness to PDGF and start differentiating into oligodendrocytes. If both PDGF and basic fibroblast growth factor (bFGF) are added in culture, O-2A progenitor cells keep growing without differentiation (Bogler et al., 1990).

Brief Summary Text (14):
The invention further provides a method of making a pluripotential embryonic stem cell comprising culturing primordial germ cells, embryonic ectoderm cells and/or germ cell progenitors in a composition comprising a growth enhancing amount of basic fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor to primordial germ cells under cell growth conditions, thereby making a pluripotential embryonic stem cell.

Drawing Description Text (2):
FIGS. 1A-C show the effect of growth factors on murine PGCs in culture.

Drawing Description Text (17):
FIG. 3 shows the effect of growth factors on male and female PGCs in culture. Cells were dissociated from either male (squares) or female (circles) genital ridges from 12.5 day p.c. mouse embryos and cultured on Sl.sup.4 -m220 feeder cells either alone (empty symbols) or with soluble rSF, LIF and bFGF (filled symbols). Cells were fixed and the number of AP positive cells counted. The experiment was carried out three times, with duplicate wells.

Drawing Description Text (24):
FIGS. 5A-C shows a photomicrograph of a colony of alkaline phosphatase positive cells derived in culture from an approximately 10.5 week old human embryonic testis. Following dissociation, testis cells were seeded into wells of a 24-well plate containing irradiated feeder cells (Sl.sup.4 h220) and growth factors 10 ng/ml bFGF, 60 ng/ml soluble SCF and 10 ng/ml LIF). After 5 days the cells were subcultured at a dilution of 1:4 into wells containing a feeder layer of irradiated mouse embryo fibroblasts with the same cocktail of growth factors. After 10 days the cultures were fixed and stained for alkaline phosphatase activity. The colony shown here (one of many) closely resembles colonies of alkaline phosphatase positive cells derived from primordial germ cells of the mouse embryo (see FIG. 2C). In particular, the human cells associate into tightly packed clusters (see arrow in FIG. 5C). FIGS. 5A, 5B and 5C are different magnifications of the same colony. The shadow in FIG. 5A is the edge of the well in which the cells were growing.

Detailed Description Text (4):

A "fibroblast growth factor" (FGF) as used herein means any suitable FGF. There are presently seven known FGFs (Yamaguchi et al. (1992)). These FGFs include FGF-1 (acidic fibroblast growth factor), FGF-2 (basic fibroblast growth factor), FGF-3 (int-2), FGF-4 (hst/K-FGF), FGF-5, FGF-6, FGF-7 and FGF-8. Each of the suitable factors can be utilized directly in the methods taught herein to produce or maintain ES cells. Each FGF can be screened in the methods described herein to determine if the FGF is suitable to enhance the growth of or allow continued proliferation of ES cells or their progenitors. Various examples of FGF and methods of producing an FGF are well known; see, for example, U.S. Pat. Nos. 4,994,559; 4,956,455; 4,785,079; 4,444,760; 5,026,839; 5,136,025; 5,126,323; and 5,155,214.

Detailed Description Text (5):
"Steel factor" (SF) is used herein. SF is also called stem cell factor, mast cell growth factor and c-kit ligand in the art. SF is a transmembrane protein with a cytoplasmic domain and an extracellular domain. Soluble SF refers to a fragment cleaved from the extracellular domain at a specific proteolytic cleavage site. Membrane associated SF refers to both normal SF before it has been cleaved or the SF which has been altered so that proteolytic cleavage cannot take place. SF is well known in the art; see European Patent Publication No. 0 423 980 A1, corresponding to European Application No. 90310889.1.

Detailed Description Text (14):
Also provided is a composition comprising an FGF, LIF, membrane associated SF, and soluble SF in amounts to enhance the growth of, and allow the continued proliferation of primordial germ cells and the formation of pluripotent ES cells from the primordial germ cell. This composition need not include primordial germ cells but comprises the various growth factors in amounts that promote the growth, proliferation and formation of pluripotent ES cells. Thus, this composition can be sufficient for the establishment of pluripotent ES cells from embryonic ectoderm cells or germ cells.

Detailed Description Text (15):
Also provided is a composition comprising: (a) mammalian primordial germ cells and/or germ cells and/or embryonic ectoderm cells; and (b) a fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor and soluble steel factor in amounts to enhance the growth and allow the continued proliferation of the cells and the formation of pluripotent embryonic stem cells.

Detailed Description Text (16):
Typically, the compositions of the invention include a feeder layer. Feeder layers can either be cells or cell lines cultured for the purpose of culturing pluripotent ES cells. Alternatively, feeder layers can be derived from or provided by the organ or tissue in which the primordial germ cells, embryonic ectoderm cells or germ cells are located, e.g. the gonad. Thus, if the somatic cells of the tissue or organ in which the desired cells are located are sufficient to provide the appropriate culture environment, a separate feeder layer is not required. Alternatively, the feeder cells could be substituted with extracellular matrix plus bound growth factors. Feeder layers which are representative of those which can be utilized are set forth in the Examples. Naturally, the membrane associated SF can be contained on the cells of such a feeder layer.

Detailed Description Text (19):
Alternatively, FGF, LIF, and SF can be used to maintain ES cells. The amounts of FGF, LIF and SF necessary to maintain ES cells can be much less than that required to enhance growth or proliferation to become ES cells. However, the cells may be maintained on a feeder layer without the addition of growth factors. Optimally, LIF can be added to enhance maintenance.

Detailed Description Text (22):
The invention also provides a method of making a mammalian pluripotential embryonic stem cell comprising culturing a germ cell or a composition from postnatal mammalian testis in a composition comprising a growth enhancing amount of basic fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor, thereby making a pluripotential embryonic stem cell from a germ cell. "Germ cells" as used herein means the cells which exist in neonatal or postnatal testis and are the progenitors of gametes. In the testis, these germ cells represent a

small population of stem cells capable of both self-renewal and differentiation into mature spermatogonia. Thus, "germ cells" are the postnatal equivalent to the prenatal primordial germ cells and can include primitive or immature spermatogonia such as type A spermatogonia or any undifferentiated early stage cell that can form a pluripotent embryonic stem cell.

Detailed Description Text (27):
FGF, SF and LIF have been shown herein to be critical for making ES cells. However, as noted above for FGF, other members of the respective growth factor family could also be used to make ES cells. Thus, later discovered members of each family can merely be substituted to determine if the new factor enhances the growth and allows the continued proliferation of PGCs or embryonic ectoderm cells to form ES cells. For example, if a new member of the LIF family is discovered, the new LIF is merely combined with SF and FGF to determine if the new family member enhances the growth and allows the continued proliferation of PGCs or embryonic ectoderm cells. Thus, this invention provides the use of family members and a method of screening family members for activity.

Detailed Description Text (28):
Likewise, additional growth factors may be found useful in enhancing the growth and proliferation of PGCs or embryonic ectoderm cells from various animals. This invention provides combining FGF, SF and LIF with other growth factors to obtain or enhance the production of ES cells. Thus, a method of screening other growth factors for the ability to promote PGCs and embryonic ectoderm cells to form ES cells is also provided. In this regard, IL-11, IL-6, CNTF, NGF, IGFII, flt3/flk-2 ligand and members of the Bone Morphogenetic Protein family are good screening candidates and can be used to promote ES cell formation.

Detailed Description Text (35):
Embryos were from ICR females mated with (C57BLxDBA)F1 males. Noon of the day of plug is 0.5 day post coitum (p.c.). The caudal region of 8.5 day p.c. embryos (between the last somite and the base of the allantois) was dissociated into single cells by incubation at 37.degree. C. with 0.05% trypsin, 0.02% EDTA in Ca.sup.++ /Mg.sup.++ free Dulbecco's phosphate-buffered saline (PBS) for about 10 mins with gentle pipetting. At this stage there are between about 149 and 379 PGCs in each embryo (Mintz and Russell, 1957). Cells from the equivalent of 0.5 embryo were seeded into a well containing feeder cells as above and 1 ml of DMEM, 2 mM glutamine, 1 mM sodium pyrovale, 100 i.u./ml penicillin and 100 ug/ml streptomycin and 15% fetal bovine serum (PGC culture medium). Finely minced fragments of genital ridges from 1.5 and 12.5 day p.e. embryos were trypsinized as above and plated at a concentration of 0.1 embryo per well. Growth factors were added at the time of seeding, usually at the following concentrations, which were shown to be optimal for PGC proliferation; recombinant human LIF and bFGF (10-20 ng/ml) and soluble rat SF (60 ng/ml). The medium was changed every day.

Detailed Description Text (46):
Culture of murine PGCs in the presence of growth factors

Detailed Description Text (47):
Initial experiments used Sl/Sl.sup.4 cells derived from a homozygous null Sl/Sl mutant mouse as a feeder layer for the culture of cells dissociated from the posterior of 8.5 days p.c. embryos, and AP staining as a marker for PGCs (FIG. 1A). As shown previously (Matsui et al., 1991), soluble SF and LIF act synergistically on PGCs. Addition of bFGF further enhances growth, and the cells continue to increase in number until day 5 in culture, i.e. one day longer than usual. The effect of bFGF alone is small, and both SF and LIF are needed in addition to bFGF for maximal effect on PGC growth (FIG. 1A, B). A variety of other growth factors, including human activin, Bone Morphogenetic Protein-4, .beta.NGF, and PDGF at 10 and 50 ng/ml had no effect in the presence of SF and LIF.

Detailed Description Text (50):
To determine whether PGCs and their descendants continue to proliferate in culture, primary colonies of PGCs were trypsinized after 6 days in culture and replated on a fresh Sl.sup.4 -m220 feeder layer with added growth factors. By day 6 in secondary culture, large colonies of densely packed AP positive cells resembling embryonic stem

(ES) cells are present (FIG. 2D,E; FIG. 4, A), with an overall plating efficiency of about 5%. These colonies are also positive for the expression of the antigen SSEA-1, a characteristic of PGCs (Donovan et al., 1986) and undifferentiated embryonal carcinoma and ES cells (Solter and Knowles, 1978) (FIG. 2 G, H). Although the growth of primary cultures is strictly dependent on the presence of LIF and bFGF, secondary colonies can form in the absence of these factors (Table 1), indicating a reduced exogenous growth factor requirement for the descendants of PGCs after subculture. Most of the colonies show strong, uniform AP staining. However, some colonies contain only a small number of strongly stained cells, surrounded by cells which are weakly stained or negative (FIG. 2E). In many cases these negative cells are larger and have a more flattened morphology than the AP positive cells. For further subculture, individual colonies of cells with a distinctive, tightly packed, ES cell-like morphology were picked up in a micropipet, trypsinized and replated on a fresh feeder layer with added factors. Such colonies can be subcultured at least ten times and continue to give rise to colonies of similar morphology. In later passages, these cultures were transferred to feeder layers of STO cells in medium without added factors normally used for blastocyst-derived ES cell culture (Robertson, 1987). Under these conditions they continue to proliferate in an undifferentiated state, for a total of at least 20 passages.

Detailed Description Text (62):
Cultures are initiated as described above by dissecting C57BL/6 8.5 days p.c. embryos free of extraembryonic tissues. Fragments comprising the posterior third of the embryo (from the base of the allantois to the first somite) are then pooled, rinsed with Dulbecco's Ca.sup.++.Mg.sup.++ free phosphate buffered saline (PBS) and dissociated with 0.25% trypsin, 1 mM EDTA (GIBCO) and gentle pipetting. This single cell suspension is then plated in 0.1% gelatin coated 24 well dishes (Coming) with irradiated Sl/Sl.sup.4 m220 cells as feeder layers at a concentration of approximately 0.5 embryo equivalents per well. The cultures were grown in Dulbecco's modified Eagle's medium (DMEM) (Specialty Media, Lavallette, N.J.) supplemented with 0.01 mM non-essential amino acids (GIBCO), 2 mM glutamine (GIBCO), 50 .mu.g/ml gentamycin (Sigma), 15% fetal bovine serum (selected batches, Hyclone) and 0.1 mM 2-mercaptoethanol (Sigma). For these primary cultures, the medium is additionally supplemented with soluble recombinant rat SF at 60 ng/ml, bFGF at 20 ng/ml (GIBCO), and LIF at 20 ng/ml. After 6 days some of the cultures are stained for alkaline phosphatase (AP) as described above in order to assess the survival and proliferation of PGCs. After 10 days, parallel cultures are dissociated into single cells and plated onto mouse embryo fibroblast (reef) feeder layers with LIF (ESGRO, GIBCO 1000 U/ml). These cultures are monitored for the appearance of colonies of EG cells. Individual EG colonies are isolated with a micropipette and lines established. EG cultures are then maintained in the same manner as ES cell lines with irradiated mefs as feeder cells and LIF (Smith et al., 1988 and Williams et al., 1988).

Detailed Description Text (68):
ES cells from other mammals can be produced using the methods described above for murine. The mammalian cell of choice is simply substituted for murine and the murine methods are duplicated. The appropriate species specific growth factors (e.g. SF) can be substituted for murine growth factors as necessary. Any additional growth factors which can promote the formation of ES cells can be determined by adding the growth factors to FGF, LIF, and SF as described above and monitored for an affect on ES formation.

Detailed Description Text (70):
The above methods for isolation of ES cells from murine embryos were repeated for isolation of ES cells from human embryos. Specifically, testes were dissected from a 10.5 week human embryo. Younger or older embryos represent alternative sources. The preferred age range is between 8.5 weeks and 22 weeks. Tissue was rinsed in buffered saline, and incubated in trypsin solution (0.25% trypsin, 1 mM EDTA in Ca.sup.30 + /Mg.sup.++ free HEPES buffered saline) for 10 minutes at 37.degree. C. The tissue was dissociated by pipetting and the cells plated into wells of a 24 well tray containing irradiated feeder cells. In this experiment the feeder cells were Sl/Sl mouse fibroblasts transfected with human membrane associated Stem Cell Factor (Sl.sup.4 h220 cells from Dr. David Williams, HHMI, Indiana State University School of Medicine). An alternative feeder layer would consist of a mixture of mouse or human embryo fibroblasts and Sl.sup.4h220 cells, to provide a more coherent layer for long term

cell attachment. The culture medium consists of Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum supplemented with 10 ng/ml human bFGF, 60 ng/ml human Stem Cell Factor and 10 ng/ml human LIF. Alternatively, the amounts of bFGF can be increased (e.g. 20 ng/ml). Other alternative or additional supplements can be added at this time, for example IF-6, IL-11, CNTF, NGF, IGFII, flt3/flk2 ligand, and/or members of the Bone Morphogenetic Protein family. The cultures were maintained for 5 days, with daily addition of fresh growth factors. Longer culture could also be utilized, e.g. 5 to 20 days.

Detailed Description Text (71):
After 5 days, cultures were dissociated with trypsin solution as before and seeded into wells containing a feeder layer of irradiated mouse embryo fibroblasts. The medium was supplemented with growth factors daily as above. The addition of growth factors to the culture medium at this stage can be utilized, and a feeder layer of a mixture of mouse of human fibroblast and Sl.sup.4 h220 cells can be substituted.

Detailed Description Text (80):
Bogler, O., Wren, D., Barnett, S. C., Land, H. and Noble, M. (1990). Cooperation between two growth factors promotes extended self-renewal and inhibits differentiation of oligodendrocyte-type-2 astrocyte (O-2A) progenitor cells. Proc. Natl. Acad. Sci. USA. 87, 6368-6372.

Detailed Description Text (81):
Dolci, S., Williams, D. E., Ernst, M. K., Resnick, J. L., Brannan, C. I., Lock, L. F., Lyman, S. D., Boswell, H. S. and Donovan, P. J. (1991). Requirement for mast cell growth factor for primordial germ cell survival in culture. Nature 352, 809-811.

Detailed Description Text (93):
Noble, M., Murray, K., Stroobant, P., Waterfield, M. D. and Riddle, P. (1988). Platelet-derived growth factor promotes division and motilty and inhibits premature differentiation of the oligodendrocyte/type-2 astrocyte progenitor cell. Nature 333, 560-562.

Detailed Description Text (95):
Raff, M. C., Lillien, L. E., Richardson, W. D., Burne, J. F. and Noble, M. D. (1988). Platelet-derived growth factor from astrocytes drives the clock that times oligodendrocyte development in culture. Nature 333, 562-565.

Detailed Description Text (107):
Yamaguchi, T. P., Conlon, R. A., and J. Rossant (1992). Expression of the fibroblast growth factor receptor FGFR-1/flg during gastrulation and segmentation in the mouse embryo. Development 152:75-88.

Detailed Description Paragraph Table (1):
TABLE 1 _______________________________________ Growth Factor Requirements for Secondary Cultures of PCG-Derived CeIIs SF .fwdarw. SF + SF + LIF + Days in LIF + LIF + bFGF .fwdarw. S SF + LIF + bFGF .fwdarw. S Culture bFGF F + LIF + bFGF F _______________________________________ 1 112 .+-. 16 cells 116 .+-. 20 cells 142 .+-. 18 cells 3 0.9 .+-. 0.6 colonies 4.6 .+-. 1.1 colonies 5.6 .+-. 0.8 colonies 5 0.5 .+-. 0.4 6.9 .+-. 1.2 colonies 6.6 .+-. 1.3 colonies colonies _______________________________________ PGCs from 8.5 dpc embryos were cultured for 6 days on SI.sup.4 -m220 cell in the presence of either soluble rat SF alone or with soluble rat SF, LIF, an bFGF. Cultures were trypsinized and seeded into wells containing SI.sup.4 -m220 feeder cells with either soluble rat SF alone or soluble rat SF, LIF, and bFGF. Cultures were fixed and APpositive cells (day 1) o colonies (days 2 and 5) counted. Numbers are mean .+-. SEM from four experiments. Secondary cultures show a reduced growth factor requirement compared with primary cultures.

CLAIMS:

1. An isolated non-murine mammalian pluripotential cell wherein said cell exhibits the following characteristics:

(a) can be maintained on feeder layers for at least 20 passages; and

(b) gives rise to embryoid bodies and differentiated cells of multiple phenotypes in monolayer culture; and wherein said cell is derived from a primordial germ cell by the process of:

(1) culturing a non-murine mammalian primordial germ cell in a composition comprising basic fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor;

(2) selecting cells that have characteristics (a) and (b), above, and

(3) isolating said non-murine pluripotential cell.

6. An isolated human pluripotential cell wherein said cell exhibits the following characteristics:

(a) can be maintained on feeder layers for at least 20 passages; and

(b) gives rise to embryoid bodies and differentiated cells of multiple phenotypes in monolayer culture; and wherein said cell is derived from a human primordial germ cell by the process of:

(1) culturing a human primordial germ cell in a composition comprising basic fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor;

(2) selecting cells that have characteristics (a) and (b), above, and

(3) isolating said human pluripotential cell.

7. A composition comprising:

(A) a human pluripotential cell derived from a primordial germ cell wherein said cell exhibits the following characteristics:

(1) can be maintained on feeder layers for at least 20 passages; and

(2) gives rise to embryoid bodies and differentiated cells of multiple phenotypes in monolayer culture; and wherein said cell is derived from a primordial germ cell by the process of:

(a) culturing a human primordial germ cell in a composition comprising basic fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor;

(b) selecting cells that have characteristics (a) and (b), above, and

(c) isolating said human pluripotential cell; and

(B) a fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor, each in amounts sufficient to permit continued proliferation of said cell.

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L6: Entry 82 of 83 File: USPT Jul 23, 1991

DOCUMENT-IDENTIFIER: US 5034515 A
TITLE: Staphylococcal fibronectin receptor, monoclonal antibodies thereto and methods of use

Brief Summary Text (5):
It has been found that S. aureus interacts with a host protein called "fibronectin." Fibronectin is a major component of the material found between cells and also in blood plasma. Fibronectin is essential to the well-being of the host as it serves as the "glue" which links one cell to another cell and plays a major role in wound healing.

Detailed Description Text (9):
The FN-R polysaccharide employed was harvested from the surface of a strain expressing large numbers of FN-R (S. aureus strain 6850) (ATCC No. 53657). This strain was discovered by screening several hundred strains of S. aureus. The FN-R polysaccharide was purified as described above. The lyophilized polysaccharide was resuspended in distilled water to a concentration of 1 mg/ml. It was then tested for inhibitory activity in a standard binding assay and adjusted to a concentration that gave 50% inhibition of 3 .mu.g 125 I-labeled fibronectin binding to 5.times.10.sup.8 S aureus ATCC 25923 (this is generally about 1 .mu.g of polysaccharide.) Then 10.mu.g of this FN-R polysaccharide which was to serve as the antigen was placed in each well of a 96 well microtiter plate and allowed to dry overnight. Antibody, either from the patient's serum or added as control, was then added to the well. Sera were pretreated with gelatin-Sepharose to remove plasma fibronectin. One microgram of fibronectin was then added to each well. After a 60 minute incubation at room temperature, the wells are washed and an alkaline phosphatase conjugated to rabbit anti-fibronectin monoclonal antibody is added. After incubation, the wells were washed again and the appropriate substrate is added.

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L12: Entry 10 of 11 File: USPT Nov 24, 1998

DOCUMENT-IDENTIFIER: US 5840334 A
TITLE: Self-binding shearform compositions

Detailed Description Text (56):
The bio-affecting agent used may be selected from a broad range of drug, therapeutic or prophylactic materials. Representative classes of drugs include those in the following therapeutic categories: ace-inhibitors; anti-anginal drugs; anti-arrythmia agents; antiasthmatics; anticholesterolemics; anticonvulsants; antidepressants; antidiarrheal preparations; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimaniacs; antinauseants; antistroke agents; antithyroid preparations; anabolic drugs; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants' decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vertigo agents; vitamins; wound healing agents; and others.

Detailed Description Text (57):
Bio-affecting agents which may be used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; atenolol; bacitracin; balsam peru; BCNU (carmustine); beclomethasone diproprionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; bethanechol; biotin; bisacodyl; bomyl acetate; bromopheniramine maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine maleate; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clonidine and its hydrochloride salt; clorfibrate; cocoa butter; cod liver oil; codeine and codeine phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; danthron; dexbromopheniramine maleate; dextromethorphan hydrobromide; diazepam; dibucaine; diclofenac sodium; digoxin; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine hydrochloride; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; efaroxan; enalapril; enoxacin; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; ferrous fumarate, gluconate and sulfate; fluoxetine and its hydrochloride; 5-fluorouracil (5-FU); flurbiprofen; folic acid; fosphenytoin; furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; griseofulvin; growth hormone; guafenesin;

hexylresorcinol; hydrochlorothiazide; hydrocodone bitartrate; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loratadine; lovastatin; luteinizing hormore; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metronidazole and its hydrochloride; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its sodium salt; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerine; nonoxynol-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine hydrochloride; phenylpropanolamine and its hydrochloride salt; phenytoin; phenelzine sulfate; pirmenol; piroxicam; polymicin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; proxephene and its HCl salt; propoxyphene napsylate; pramiracetin; pramoxine and its hydrochloride salt; propanolol HCl; pseudoephedrine hydrochoride and sulfate; pyridoxine; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; tacrine and its HCl salt; theophylline; terfinidine; thioperidone; trimetrexate; triazolam; timolol maleate; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; tripolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B.sub.1, B.sub.2, B.sub.6, B.sub.12, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

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L12: Entry 9 of 11 File: USPT Feb 9, 1999

DOCUMENT-IDENTIFIER: US 5869098 A
TITLE: Fast-dissolving comestible units formed under high-speed/high-pressure conditions

Brief Summary Text (80):
peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vertigo agents; vitamins; wound healing agents; and others.

Brief Summary Text (81):
Bio-affecting agents which may be used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate; carbonate; chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; atenolol; bacitracin; balsam peru; BCNU (carmustine); beclomethasone diproprionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; bethanechol; biotin; bisacodyl; bornyl acetate; bromopheniramine maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine maleate; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clonidine and its hydrochloride salt; clorfibrate; cocoa butter; cod liver oil; codeine and codeine phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; danthron; dexbromopheniramine maleate; dextromethorphan hydrobromide; diazepam; dibucaine; diclofenac sodium; digoxin; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine hydrochloride; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; efaroxan; enalapril; enoxacin; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; ferrous fumarate, gluconate and sulfate; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine and its hydrochloride; flubiprofen, furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; griseofulvin; growth hormone; guafenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone bitartrate; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loratadine; lovastatin; luteinizing hormore; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metronidazole and its hydrochloride; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its sodium salt; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerine; nonoxynol-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione; pentastatin; peppermint oil; pentaerythritol

tetranitrate; pentobarbital sodium; pheniramine maleate; phenobarbital; phenol;

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L12: Entry 8 of 11 File: USPT Nov 9, 1999

DOCUMENT-IDENTIFIER: US 5980941 A
TITLE: Self-binding shearform compositions

Brief Summary Text (73):
The active ingredients useful herein can be selected from a large group of therapeutic agents. Respective classes include those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthinatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antiulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Brief Summary Text (74):
Active agents which may be used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone diproprionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subsalicylate; bornyl acetate; bromopheniramine and its maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; centrizine and its hydrochloride; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fiumarate; clonidine and its hydrochloride salt; clorfibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine and its hyddrochloride; danthron; dexbromopheniramine maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; dihydroergotamine and

its hydrogenates/mesylates; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efaroxan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine and its hydrochloride; flurbiprofen; furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron and its hydrochloride; griseofulvin; growth hormone; guafenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loratadine; lovastatin; luteinizing hormore; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; meclizine and its hyddrochloride; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metoclopramide and its halides/hydrates; metronidazole and its hydrochloride; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nimesulide; nitroglycerine; nonoxynol-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron and its hydrochloride; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides; phenylpropanolamine and its hydrochloride salt; phenytoin; pirmenol; piroxicam and its salts; polymicin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its hydrochloride; propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its hydrochloride salt; prochlorperazine and its maleate; propanolol and its hydrochloride; promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and hydrochorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and its succinate; tacrine and its hydrochloride; theophylline; terfenadine; thiethylperazine and its maleate; timolol and its maleate; thioperidone; tramadol; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride; tollmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripelennamine and its hydrochloride; tripolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B.sub.1, B.sub.2, B.sub.6, B.sub.12, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

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L12: Entry 7 of 11 File: USPT Jan 11, 2000

DOCUMENT-IDENTIFIER: US 6013280 A
TITLE: Immediate release dosage forms containing microspheres

Detailed Description Text (9):
The active ingredients useful herein can be selected from a large group of therapeutic agents. Respective classes include those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthmatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatories; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antiulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Detailed Description Text (10):
Active agents which may be used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; astemizole; atenolol; azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone diproprionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subsalicylate; bornyl acetate; bromopheniramine and its maleate; buspirone; caffeine; calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; centrizine and its hydrochloride; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine and its hydrochloride salt; clorfibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine and its hyddrochloride; danthron; dexbromopheniramine maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; dihydroergotamine and

its hydrogenates/mesylates; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docusate calcium, potassium, and sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efaroxan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine and its hydrochloride; furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron and its hydrochloride; griseofulvin; growth hormone; guafenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; loratadine; lovastatin; luteinizing hormore; LHRH (lutenizing hormone replacement hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; meclizine and its hyddrochloride; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide; metoclopramide and its halides/hydrates; metronidazole and its hydrochloride; metoprotol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerine; nonoxynol-9; norethindrone and its acetate; nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; ondansetron and its hydrochloride; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and hydrochlorides; phenylpropanolamine and its hydrochloride salt; phenytoin; pirmenol; piroxicam and its salts; polymicin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; promethazine and its hydrochloride; propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its hydrochloride salt; prochlorperazine and its maleate; propanolol and its hydrochloride; promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and hydrochorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate, and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; sumatriptan and its succinate; tacrine and its hydrochloride; theophylline; terfenadine; thiethylperazine and its maleate; timolol and its maleate; thioperidone; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripelennamine and its hydrochloride; tripolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B.sub.1, B.sub.2, B.sub.6, B.sub.12, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate. Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

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L12: Entry 5 of 11 File: USPT Apr 25, 2000

DOCUMENT-IDENTIFIER: US 6054298 A
TITLE: Fringe proteins and pattern formation

Detailed Description Text (24):
A further use of the invention concerns the therapeutic application of a fringe protein, or an agonist or antagonist thereof, to enhance survival of or increase the differentiation of particular tissues or cells in various systems throughout the body. The ability of fringe to regulate differentiation during development and also presumably in the adult state indicates that fringe can be reasonably expected to facilitate control of adult cells with regard to maintenance, functional performance and aging of normal cells; repair and regeneration processes in chemically or mechanically lesioned cells; and prevention of degeneration and premature death which result from a loss of differentiation in certain pathological conditions. In light of this knowledge, the present invention can be used in the treatment of, prevention and/or reduction of the severity of various disorders, including disorders of the vasculature system such as varicosities and atherosclerosis. Particularly since the subject fringe proteins appear to be involved in committing cells to form blood vessels, the fringe proteins of the present invention can also be used in the treatment of tumor pathogenesis, i.e., the ability to block the activity of the fringe proteins can be useful in preventing the establishment or maintenance of the blood supply to solid tumors. The fringe proteins of the present invention are also useful in wound healing, in that the augmentation of fringe activity, and thus the augmentation of angiogenesis, may aid in speeding the recovery of wounded regions of the body.

Detailed Description Text (47):
Following hybridization, embryos were washed three times for 3 minutes each time at 70.degree. C. with solution 1 (50% formamide, 5.times.SSC, 1% SDS [pH 4.5]), three times for 30 minutes each time at 70.degree. C. with solution 3 (50% formamide, 2.times.SSC [pH 4.5]), and three times at room temperature with tris-buffered saline (TBS, with 2 mM levamisole) containing 1% Tween 20. Nonspecific binding of antibody was prevented by preblocking embryos in TBS plus 1% Tween 20 containing 10% heat-inactivated sheep serum for 2.5 hours at room temperature and by preincubating anti-digoxigenin Fab alkaline phosphatase conjugate (Boehringer Mannheim) in TBS plus 1% Tween 20 containing heat-inactivated 1% sheep serum and approximately 0.3% heat-inactivated chick embryo powder. After an overnight incubation at 4.degree. C. with the preadsorbed antibody in TBS plus 1% Tween 20 containing 1% sheep serum, embryos were washed three times for 5 minutes each time at room temperature with TBS plus 1% Tween 20, five times for 1.5 hours each time at room temperature with TBS plus 1% Tween 20, and overnight with TBS plus 1% Tween 20 at 40.degree. C. The buffer was exchanged by washing three times for 10 minutes each time with NTMT (100 mM NaCl, 100 mM Tris-HCl, 50 mM MgCl.sub.2, 1% Tween 20, 2 mM levamisole). The antibody detection reaction was performed by incubating embryos with detection solution (NTMT with 0.25 mg/ml nitroblue tetrazolium and 0.13 mg/ml 5-bromo-4-chloro-3-indolyl-phosphate toluidinium). In general, prelimb bud stage embryos were incubated for 5-15 hours and limb bud stage embryos for 1-5 hours. After the detection reaction was deemed complete, embryos were washed twice with NTMT, once with PBT (pH 5.5), postfixed with 4% paraformaldehyde/0.1% glutaraldehyde in PBT, and washed several times with PBT. In some cases, embryos were cleared through a series of 30%, 50%, 70% and 80% glycerol in PBT. Whole embryos were photographed under transmitted light using a Nikon zoom stereo microscope with Kodak Ektar 100 ASA film. Selected embryos were processed for frozen sections by dehydration in 30% sucrose in PBS followed by embedding in gelatin and

freezing. Cryostat sections (25 .mu.m) were collected on superfrost plus slides (Fisher), rehydrated in PBS, and mounted with gelvatol. Sections were photographed with Nomarski optics using a Zeiss Axiophot microscope and Kodak Ektar 25 ASA film.

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L17: Entry 22 of 22 File: USPT May 2, 1995

DOCUMENT-IDENTIFIER: US 5411882 A
TITLE: Cytokine which mediates inflammation

Detailed Description Text (126):
Suitable culture media for the expansion of hybridoma cells are the standard culture media, such as Dulbecco's modified Eagle medium (DMEM), minimum essential medium, RPMI 1640 medium and the like, optionally replenished by a mammalian serum, e.g. 10 to 15% fetal calf serum. Preferentially, feeder cells, e.g. normal mouse peritoneal exudate cells, spleen cells, bone marrow macrophages or the like, are added at the beginning of cell growth immediately after the fusion step to nourish the hybridoma cells and support their growth, especially where cell densities are low, by providing growth factors and the like. If phagocytic cells such as macrophages or monocytes are used, they can perform a helpful service in cleaning up the debris of dead myeloma cells always found after aminopterin treatment. The culture media are supplemented with selective medium in order to prevent myeloma cells from overgrowing the hybridoma cells.

Detailed Description Text (249):
Aliquots of the cellular lysates and culture supernatants of the mock transfectant 3AB, of the parental transfectant 2B1 and of the MTX treated clones 2B1-B4C2 and 2B1-B4E3 are tested for their concentration of rMRP-70 and MRP-160 with the two-site enzyme linked immunosorbent assay (ELISA) described in the following. The ELISA is performed using the affinity purified rabbit anti-rMRP-70 antibodies of Example 14.2 following standard protocols (E. Engvall and P. Periman, immunochem. 8, 87 1, 1971; J. Brueggen et at., Cancer Immunol. Immunother. 15, 200, 1983). Rabbit anti-rMRP-70 IgG (1.0 .mu.g/ml) in 0.05M carbonate buffer pH 9.6 is coated at 100 .mu.l/well into 96-well plates (Nunc FI) and incubated overnight at 4.degree. C. After blocking the nonspecific sites with Iris buffered saline (TBS, 0.05M, pH 7.4) containing 0.2% gelatin (Biorad), 1.0% bovine serum albumin (Serva) and 0.05% Tween.RTM. 20 (Biorad) for 1 hr at room temperature, the test samples (50 .mu.l), recombinant rMRP-70 standards (1.9-250 ng/ml, see Example 9) and controls diluted in blocking buffer are added for 1 hr at 37.degree. C. The plates are washed (Skatron Microwash II) with TBS containing biotinylated anti-rMRP-70 IgG (50 .mu.l, 0.5 .mu.g/ml; biotinylation according to a modified protocol of Lerner et al., J. Exp. Med. 152, 1085, 1980) for 30 min at 37.degree. C. After washing, 50 .mu.l of streptavidin alkaline phosphatase conjugate (Gibco BRL) is added for 30 min at 37.degree. C. The bound enzyme is incubated with 100 .mu.l of p-nitrophenyl phosphate (1.0 mg/ml in diethanolamine buffer 1M, pH 9.8; Sigma) for 30 min at ambient temperature, and then stopped with 0.5 N HCl. The absorbances are read at 405 nm (Multiscan MCC, Flow). The data are reduced using a 4-parameter logistic curve fitting program (Flow).

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L17: Entry 21 of 22 File: USPT Sep 5, 1995

DOCUMENT-IDENTIFIER: US 5447862 A
TITLE: Pectin lyase genes of aspergillus niger

Brief Summary Text (51):
Examples of such heterologous structural genes are e.g. those coding for hormones such as secretin, thymosin, relaxin, calcitonin, luteinizing hormone, parathyroid hormone, adrenocorticotropin, melanocyte-stimulating hormone, .beta.-lipotropin, urogastrone or insulin, growth factors, such as epidermal growth factor, insulin-like growth factor (IGF), e.g. IGF-I and IGF-II, mast cell growth factor, nerve growth factor, glia derived nerve cell growth factor, or transforming growth factor (TGF), such as TGFB, growth hormones, such as human or bovine growth hormones, interleukin, such as interleukin-1 or -2, human macrophage migration inhibitory factor (MIF), interferons, such as human .alpha.-interferon, for example interferon-.alpha.A, .alpha.B, .alpha.D or .alpha.F, .beta.-interferon, .gamma.-interferon or a hybrid interferon, for example an .alpha.A-.alpha.D- or an .alpha.B-.alpha.D-hybrid interferon, especially the hybrid interferon BDBB consisting, in the order from N- to C-terminus, of the first and second domains (B.sub.1, corresponding to amino acids 1 to 60, and B2, corresponding to amino acids 61 to 92) of human interferon aB, of the third domain (D.sub.3, corresponding to amino acids 93 to 150) of human interferon aD and of the fourth domain (B.sub.4, corresponding to amino acids 151 to 166) of human interferon aB, proteinase inhibitors such as .alpha..sub.1 -antitrypsin, SLPI and the like, hepatitis virus antigens, such as hepatitis B virus surface or core antigen or hepatitis A virus antigen, or hepatitis nonA-nonB antigen, plasminogen activators, such as tissue plasminogen activator or urokinase, tumour necrosis factor, somatostatin, renin, .beta.-endorphin, immunoglobulins, such as the light and/or heavy chains of immunoglobulin D, E or G, or human-mouse hybrid immunoglobulins, immunoglobulin binding factors, such as immunoglobulin E binding factor, calcitonin, human calcitonin-related peptide, blood clotting factors, such as factor IX or VIIIc, erythropoietin, eglin, such as eglin C, hirudin, desulfatohirudin, such as desulfatohirudin variant HV1, HV2 or PA, human superoxide dismutase, viral thymidin kinase, .beta.-lactamase, glucose isomerase. Preferred genes are those coding for a human .alpha.-interferon or hybrid interferon, human tissue plasminogen activator (t-PA), hepatitis B virus surface antigen (HBVsAg), insulin-like growth factor I and II, eglin C and desulfatohirudin, e.g. variant HV1. In the hybrid vectors of the present invention, the present promoter and/or signal sequence is operably linked to the polypeptide coding region so as to ensure effective expression of the polypeptide.

Detailed Description Paragraph Table (1):
The abbreviations have the following meanings: Amp ampicillin ATP adenosine triphosphate bp base pairs BSA Bovine serum albumin cpm counts per minute (radioactive decay) dATP 2'-deoxyadenosine triphosphate dCTP 2'-deoxycytidine triphosphate dGTP 2'-deoxyguanosine triphosphate dTTP 2'-deoxytbymidine triphosphate dNTP mixture of DATP, DCTP, DGTP and DTTP CIP or alkaline phosphatase from calf intestine CIAP DNA deoxyribonucleic acid DTT 1,4-dithiothreitol EDTA ethylenediaminetetraacetic acid disodium salt EGTA bis-(aminoethyl)-glycolether)N,N,N',N'-tetraacetic acid hrs hours IPTG isopropyl-B-D-thio-galactopyranoside kb kilobases LMP low melting point min minutes mOsm milliosmoles PEG polyethyleneglykol PL pectin lyase I PTH phenylthiohydantion RF-DNA double-stranded replicative form DNA RNA ribonucleic acid RT room temperature rpm revolutions per minute SDS sodium dodecyl sulfate ss single-stranded Tc Tetracyline Tris tris(hydroxymethyl)-aminomethane tRNA transfer RNA U units .mu.g

microgram V Volt vol volume X-GAL 5-bromo-4-chloro-3-indonyl-.beta.-galactoside Buffers, media, reagents: ss-Denhardt 0.02% ficoll (Sigma), 0.02% polyvinylpyrrolidone (Sigma), 0.02% BSA (Sigma), 100 .mu.g/ml denaturated salmon sperm DNA (Sigma) HHA B/g 10X restriction-enzyme buffer used for BamHI, BglII, HindIII, MboI, PstI and XhoI digests, containing 60 mM Tris-HCl (pH 7.4), 60 mM .beta.-mercaptoethanol, 60 mM MgCl.sub.2, 500 mM NaCl, 0.1% BSA, 0.1% gelatin EcoRIbuffer 5X restriction-enzyme buffer used for EcoRI digests, containing 500 mM Tris-HCl (pH 7.2), 25 mM MgCl.sub.2, 250 mM NaCl, 0.05% BSA, 0.05% gelatin HgaI buffer 50 mM NaCl, 10 mM MgCl.sub.2, 1 mM DTT, 100 .mu.g/ml BSA, 6 mM Tris-HCl pH 7.4 (final concentration). IPTG 100 mM isopropyl-.beta.-thio-galactopyranoside (23.8 mg/ml) in H.sub.2 O LB medium 1% Bacto-tryptone (Difco), 0.5% Bacto yeast extract (Difco), 170 mM NaCl, adjusted to pH 7.5 with NaOH LC medium 1% trypticase peptone (BBL), 0.5% yeast extract (BBL), 0.8% NaCl, 1 ml Tris-HCl pH 7.5 per litre ligation buffer 20 mM Tris-HCl, 10 mM MgCl.sub.2, 10 mM dithioerythritol, 0.6 mM ATP, pH 7.6 minimal medium 1.05% K.sub.2 HPO.sub.4, 0.45 KH.sub.2 PO.sub.4, 0.1% (NH.sub.4).sub.2 SO.sub.4, 0.05% for E. coli sodium citrate. 2H.sub.2 O, 1 mM MgSO.sub.4, 1 mM thiamine-HCl, 0.2% glucose 2XTY medium per litre 16 g trypticase peptone (BBL), 10 g yeast extract, 5 g NaCl TBE-buffer 1 litre contains 10.8 g Tris, 5.5 g boric acid, 4 ml 0.5 M EDTA (pH 8.0) TE buffer 10 mM Tris-HCl (pH 8.0), 1 mM EDTA (pH 8.0) low TE buffer 10 mM Tris-HCl (pH 8.0), 0.1 mM EDTA (pH 8.0) X-gal or X-GAL 2% (5-bromo-4-chloro-3-indolyl-.beta.- galactoside) in dimethylformamide SSC 0.15 M NaCl, 0.015 M sodium citrate SOC medium 2% Bacto Tryptone (Gibco), 0.5% Yeast- Extract (Gibco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl.sub.2, 5 mM MgSO.sub.4, 20 mM Glucose kinase buffer 50 mM Tris-HCL, 10 mM MgCl.sub.2 5 mM DDT (pH 7.5) X-gal plates 0.002% X-Gal, 0.07 mM IPTG NET 0.15 M NaCl, 0.015 M Tris.HCl (pH 7.5) 1 mM EDTA minimal medium 0.6% Na.sub.2 HPO.sub.4, 0.1% NH.sub.4 Cl, 0.05% NaCl, for E. coli 1 mM MgSO.sub.4, 0.01 mM CaCl.sub.2, 1 mM thiamine-HCl, 0.2% glucose minimal medium 1 litre contains 1.5 g KH.sub.2 PO.sub.4, 0.5 g KCl, for A. niger 0.5 g MgSO.sub.4.7H.sub.2 O, 4.0 g NH.sub.4 Cl, 10.0 g glucose, traces of FeSO.sub.4,, MnSO.sub.4, ZnCl.sub.2, adjusted to pH 6.5 with NaOH complete medium Mycophil-Agar (BBL) or minimal for A. niger medium plus 0.2% trypticase peptone for (BBL) 0.1% casaminoacids (Difco), 0.1% yeast extract (BBL), 0.05% ribonuleic acid sodium salt from yeast (ICN, Cleveland, USA), 2 ml vitamin solution per litre vitamin solution per 100 ml 10 mg thiamine, 100 mg riboflavin, 10 mg panthotenic acid, 2 mg biotin, 10 mg p-aminobenzoic acid, 100 mg nicotinamide, 50 mg pyridoxin-HCl PCT 25% polyethylene glycol 6000 (Merck, Darmstadt) in 10 mM Tris-HCl (pH 7.5), 50 mM CaCl.sub.2 sporulation medium 10 g/l pbytone peptone, 10 g/l glucose, 10 g/l agar For plates all media are solidified by addition of 1.5% agar (BBL), for topagar(ose) 0.7% agar (BBL) or agarose (Seakem) is used. PBS per litre 0.37 g NaH.sub.2 PO.sub.4, 2.7 g Na.sub.2 HPO.sub.4, 4 8.5 g NaCl PSB 10 mM Tris-HCl (pH 7.6), 100 mM NaCl, 10 mM MgCl.sub.2 , 0.05% gelatine LDB 10 mM Tris-HCl (pH 7.6), 100 mM NaCl, 10 mM MgCl.sub.2 The following strains are used: A. niger N400 wildtype A. niger N593 cspA, pyrA A. niger N756 selected for high production of pectinase complex enzymes A. niger AN8 DSM 3917, uridine anxotrophic mutant of A. niger N756 E. coli NM539 metB, supE, hsdM.sup.+, hsdR.sup.- , supF, (P2cox3) E. coli MH1 ara D139, .DELTA.lacX74, galU, galK, hsr.sup.-, hsm.sup.+, strA, E. coli JM103 .DELTA.lac-pro, thi, strA, supE, endA, sbcB, hsdR4, F.sup.1, traD36, proAB, lacIq, Z.DELTA.M15 E. coli JM109 .DELTA.(lac-proAB), recA1, endA1, gyrA96, thi, hsdR17, supE44, relA1, .lambda..sup.-, [F', traD36, proAB, lacI.sup.q, Z.DELTA.M15] E. coli CJ236 (dut-1, ung-1, thi-1, relA-1; pCJ105(Cm.sup.r); BIO-RAD Muta-Gene M13 in vitro mutagenesis kit) E. coli MV1190 [.DELTA.(lac-proAB), thi, supE, .DELTA.(srl-recA)306::Tn10(tet.sup.r) (F':traD36, proAB, lac 1.sup.q Z.DELTA.M15)]. Strain MV1190 is described in the manual for the BIO-RAD MUTA-GENE M13 in vitro mutagenesis kit E. coli strain HB101: F.sup.-, hsdS20(r.sup.-.sub.B m-B), recA13, ara14, proA2, lacY1, galK2, rpsL20(str.sup.R), xyl-5, mtl-1, supE44, .lambda..sup.- (Maniatis et al. (Ret5)) E. coli strain BJ5183: F.sup.-, endA, sbcB.sup.-, recBC.sup.-, galK, met.sup.-, str.sup.R, thi-1, bioT, hsdR(r.sub.K.sup.-, m.sub.K.sup.+), .lambda..sup.- (Hanahan (37)). E. coli strain JM101: supE, thi, .DELTA.(lac-proAB), (F', traD36, proAB, lac19Z.DELTA.M15) (Yanisb-Perron et al. (47))

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L17: Entry 20 of 22 File: USPT Jun 11, 1996

DOCUMENT-IDENTIFIER: US 5525503 A
TITLE: Signal transduction via CD28

Detailed Description Text (15):
cDNA encoding full-length human fyn (Cooke et al., 1989, New Biologist 1:66-74) and the p85 subunit of PI 3-kinase was amplified by the PCR (Escobedo et al., 1991, Cell 65:75-82; Skolnick et al., 1991, Cell 65:83-90; Otsu et al., 1991, Cell 65:91-104) and cloned into the transfer vector pvl1393 (InvitroGen, San Diego, Calif.) into the Bam H1 site. Sf21 cells (InvitroGen Corp., San Diego, Calif.) were then transfected with a mixture of linear wild type baculoviral DNA (InvitroGen, San Diego, Calif.) and pVL1393-DNA constructs, and screened for recombinant virus plaques of the occlusion negative phenotype. Recombinant virus was purified from contaminating wild type virus by two rounds of plaque purification. The cells were infected with wild type or recombinant virus (multiplicity of infection=5), harvested 3 days later, and lysed in a solution of 1% Triton X-100 and 1 mM PMSF. Immunoprecipitations were carried out as described above. Following SDS-PAGE, proteins were transferred to a nitrocellulose membrane, blocked with gelatin (1% w/v), immunoblotted with anti-p85 rabbit serum (1:1000), and detected using goat anti-rabbit alkaline phosphatase, nitroblue tetrazolium (NBT) and 5-bromo-4-chloro-3-indolyl phosphate (BCIP) (Promega, Madison, Wis.).

Detailed Description Text (21):
Residues 191 to 194 within the cytoplasmic tail of CD28 correspond to the motif, Tyr-Met-X-Met, with a phosphorylated Tyr residue (Songyang et al., 1993, Cell 72:767). This sequence constitutes the optimal motif for binding of the first SH2 domain within the p85 subunit of PI 3-kinase. It is also found in a variety of other non-T cell receptors (PDGF-R, CSF-1, c-KIT) and intracellular binding proteins (insulin receptor substrate-1 (IRS-1), Polyoma Middle T antigen), as shown in Table 1. Each of these receptors has been found to bind to PI 3-kinase by means of the Tyr-Met-X-Met motif (Sun et al., 1991, Nature 318:183; Lev et al., Proc. Natl. Acad. Sci. USA 89:678; Girogetti et al, J. Biol. Chem. 268:7328; Bjorge et al., 1990, Proc. Natl. Acad. Sci. USA 87:3816; Backer et al., 1992, The EMBO J. 11:3469; Kashinshian et al.,1992, The EMBO J. 11:1373; Tuveson et al., Science 260:986.

Detailed Description Text (30):
The cytoplasmic tail of CD28 contains an amino acid sequence fitting the motif, Tyr-Met-X-Met (SEQ ID NO:1), found in other receptors that bind to PI 3-kinase (see Table 1 and FIG. 7). This motif is the optimal binding motif for the SH2 domain of PI 3-kinase found in a variety of other receptors and intracellular proteins, including the platelet-derived growth factor receptor (PDGF-R), colony stimulating factor-1 receptor (CSF-1-R), the Polyoma virus middle T antigen and the IRS-1.

Detailed Description Text (36):
CD28 is now known to be one of several proteins which lack endogenous tyrosine kinase activity, and which bind to PI 3-kinase. Others include middle T antigen of Polyoma virus, the insulin IRS protein, and the CD19 antigen, each of which possess a Tyr-Met-X-Met motif. The CD28-PI 3-kinase association provides an alternative mechanism by which the T-cell receptors may interact directly with PI 3-kinase, in contrast to the interaction of the CD4-p56.sup.lck and TcR.zeta./CD3-p59.sup.fyn with PI 3-kinase which is mediated by the SH3 domain of the tyrosine kinase. Thus, CD28 binding to PI 3-kinase differs from the mechanism used by src kinases in recruiting the enzyme. Furthermore, the level of PI 3-kinase activity associated with src kinases

is much lower than that associated with CD28. Thus, the mechanism of recruiting and binding PI 3-kinase utilized by the CD4-p56.sup.lck and TcR.zeta./CD3-p59.sup.fyn complexes differs fundamentally from that utilized by CD28, and the PDGF, insulin, and CSF-1 receptors.

Detailed Description Paragraph Table (1):
TABLE 1 ________ CD28 LHSD YMNN TPRRP SEQ ID NO:2 PDGF-R SDGG YXDM SKDES SEQ ID NO:3 CSF-1 R GVDT YVEM RP SEQ ID NO:4 c-KIT STNE YMDM KP SEQ ID NO:5 IRS-1 DDG YMPM SPGV SEQ ID NO:6 IRS-1 GNGD YMPM SPKS SEQ ID NO:7 IRS-1 PNG YMMM SPSG SEQ ID NO:8 IRS-1 TGD YMNM SPVG SEQ ID NO:9 IRS-1 SEE YMNM DLGP SEQ ID NO:10 Polyoma EEEE YMPM EDLYL SEQ ID NO:11 EGF-R DADE YLIP QQGFF SEQ ID NO:12 FGF-R SNQE YLDL SMPLD SEQ ID NO:13 ________

Other Reference Publication (3):
Auger et al., "PDGF-Dependent Tyrosine Phosphorylation Stimulates Production of Novel Polyphosphoinositides in Intact Cells", Cell 57:167-175 (1989).

Other Reference Publication (4):
Cochet et al., "Interaction between the Epiderman Growth Factor Receptor and Phosphoinositide Kinases", J. Biol. Chem. 2266:637-644 (1991).

Other Reference Publication (5):
Fanti et al., "Distinct Phosphotyrosines on a Growth Factor Receptor Bind to a Specific Molecular That Mediate Different Signaling Pathways", Cell 69:413-423 (1992).

Other Reference Publication (14):
Bjorge et al., "Activated Type I Phosphatidylinositol Kinase is Associated with the Epidermal Growth Factor (EGF) Receptor Following EGF Stimulation", Proc. Natl. Acad. Sci USA 87:3816-3820, 1990.

Other Reference Publication (15):
Kashishian et al., "Phosphorylation Site in the PDGF Receptor with Different Specificities for Binding GAP and P13 Kinase In Vivo," The EMBO Journal 11:1373-1382, 1992.

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L17: Entry 19 of 22 File: USPT Jul 2, 1996

DOCUMENT-IDENTIFIER: US 5532156 A
TITLE: Hepatocyte cell line derived from the epiblast of pig blastocysts

Brief Summary Text (6):
An alternative to normal parenchymal hepatocyte cell culture has been the establishment of numerous human and rodent hepatocarcinoma derived cell lines (Richardson et al., J. Cell Biol., 40: 236-247, 1969; Aden et al., Nature (London), 282: 615-616, 1970). Although several of these hepatoma cell lines were minimally deviated and expressed various proteins representative of normal hepatocyte function, they were likely to be abnormal in several aspects, particularly growth control. For example, some of these cell lines were highly tumorigenic when placed in vivo (Richardson, 1969, supra; Knowles et al., Science, 209: 497-499, 1980). Also, while hepatocyte growth factor (HGF) is mitogenic for primary hepatocytes, it has been reported to be cytostatic for the hepatoma cell lines HepG2, Hep3B, and H35 (Higashi and Shima, 1993). Some human hepatoma cell lines also chronically produced hepatitis proteins (Aden et al., 1979, supra; Knowles et al., 1980, supra). Thus, hepatoma derived cell cultures may confuse assessments of normal parenchymal hepatocyte biology in vitro, and in vivo assessments may not be possible. The ability to sustainably culture normal, functional parenchymal hepatocytes in secondary culture is therefore novel and of great value for the routine study of hepatocyte biology.

Detailed Description Text (23):
Mouse ES cells often suffer extensive cell death or differentiation if passaged in the absence of feeder cells (Robertson, E. Embryo-derived stem cell lines. In: Robertson, E., ed. Teratocarcinomas and embryonic stem cells: a practical approach. Oxford: IRL Press, 1987: 71-112). The cytokine LIF, also known as differentiation inhibitory activity (DIA), is the factor secreted from STO feeder cells which maintains mouse ES cells in an undifferentiated state (Rathjen et al., Cell, 62:1105-1114, 1990; Smith and Hooper, Exp. Cell. Res., 145: 458-462, 1983; and Williams et al., Nature, 336: 684-687, 1988). EDF (Activin-A) has also been found to suppress the differentiation of mouse EC cells (van den Eijnden-van Raaij et al., A. Mech. Dev., 33: 157-166, 1991). Neither of these cytokines had a differentiation-inhibiting effect on the pig epiblast cultures. This was the case at both the primary colony stage and with the various subcultures established after passage. Furthermore, they did not prevent rapid senescence of the PICM cell cultures when they were removed from culture with STO cells. Thus, under the culture conditions tested, the pig epiblast cells did not respond to LIF in the same manner as mouse epiblast cells. This apparent lack of anti-differentiation or proliferation response to added recombinant LIF has also been observed in certain human EC cell lines (Pera at al., Differentiation, 42: 10-23, 1989; P. Andrews, personal communication, 1992) and in the culture of pig and sheep ICM-derived cells (Piedrahita et al., Theriogenology, 34: 879-901, 1990). Although there is no direct evidence for the absence of the LIF receptor in the pig epiblast cells, the inability to maintain these cells in an undifferentiated state may depend on up-regulating the expression of the LIF receptor. If the LIF receptor is present, its function may depend on interaction with homologous pig LIF or a synergistic interaction with other growth factors. EDF had a similar lack of effect but this was not unexpected because it also failed to maintain the undifferentiated phenotype of the D3 mouse ES cell line when grown without STO feeder cells.

Detailed Description Text (25):
The pig epiblast cells of the primary and secondary cultures spontaneously differentiated into various cell types, which seem to be mesodermal, neuroectodermal,

ectodermal, and endodermal in character. As with some mouse EC cell lines, the final differentiation events of the pig epiblast cultures occurred after several weeks in maintenance culture on STO feeder cells (Nicolas et al., Cancer Res., 36: 4224-4231, 1976). It has long been recognized that the differentiation of various cells is induced by paracrine regulatory interactions or cell-to-cell interactions with mesenchymal cells (Balinsky, B. I., An introduction to embryology. Philadelphia: W. B. Saunders, 1970: 566-578; Drew, A. H., Br. J. Exp. Pathol., 4: 46-52, 1923; Gorbstein, C., Exp. Cell. Res., 13: 575-587, 1957). The differentiation of the pig epiblast cells may be driven by the STO feeder cells elaborating combinations of growth factors which do not predispose to prevent differentiation. For example, it has been shown that cultured fibroblasts secrete hepatocyte growth factor to the extent that it induces epithelial morphogenensis in co-cultured MDCK cells (Montesano et al., Cell, 67: 901-908, 1991). Also, among the known pleiotropic effects of LIF is its ability to promote the differentiation of neural crest cells and hemopoietic cells, to stimulate myoblast proliferation, and to activate hepatocytes (Hilton and Gough, J. Cell. Biochem., 46:21-26, 1991; Mummery, 1991, supra). Given this, it is very possible that co-culture on STO cells contributed to the differentiation observed in the pig epiblast cultures.

Detailed Description Text (31):
The PICM-19 cells have utility as an in vitro model for fetal hepatocyte functions (e.g., hemopoiesis) and are also useful in experimentation on artificial organ construction and gene therapy. For example, attempts have been made to utilize rat hepatocytes for the construction of bioartificial livers (Nyberg et al., Cytotechnology, 10: 205-215, 1992; Li et al., In Vitro Cell. Dev. Biol., 29A: 249-254, 1993) Since pig liver cells are physiologically more closely related to human cells than mouse or rat, the cells described herein have obvious advantages over cells of such origin as well as the obvious advantage of normal cells over tumor cells. The cell line also has significant value as a research reagent, that is, a sustainable fetal liver cell culture. Moreover, it would serve as a valuable source of novel growth factors and pharmaceuticals and for the production of viruses or vaccines (e.g., hepatitis viruses), as well as for the study of liver parasites or of parasites having a stage of development in the liver (e.g., malarial organisms), for in vitro toxicity and metabolism testing of drugs and industrial compounds, for gene therapy experimentation (since the liver is the largest vascular organ of the body), for the construction of artificial translatable livers, and for liver mutagenesis and carcinogenesis studies. In addition, the derivation of the PICM hepatocyte cultures from the pig epiblast demonstrates the possibility of deriving specialized cell types from any mammalian epiblast.

Detailed Description Text (55):
Serum-free medium [DMEM-199 with HGF (2 ng/ml), rat tail collagen (30 mg/ml), and 1.times.MITO.sup.+ serum extender (Collaborative)] was conditioned for 3 days by 50-75% confluent monolayers of PICM-19 or STO feeder cells alone. Conditioned media samples or diluted pig serum (1:50) were mixed 1:1 with loading buffer containing SDS and 2-mercaptoethanol. Samples were loaded onto a 12% polyacrylamide gradient gel and electrophoresis performed under described conditions (Laemmli, U. K., Nature, 277:680-685, 1970). Proteins were transferred to nitrocellulose (0.2.mu.), blocked with gelatin and probed with polyclonal antisera. Specific immunoreactive antigens were visualized with alkaline phosphatase conjugated secondary antibody reagents (Sigma).

Detailed Description Text (62):
The PICM hepatocyte cell cultures were all derived by co-culture on STO feeder cells. STO feeder cells were shown to provide an environment suitable for the isolation and maintenance of hepatocarcinoma cells (Aden et al., Nature (London), 282: 615-616, 1979), mouse embryonic stem cells (Robertson, 1987, supra) and mouse primordial germ cells (Matsui et al., Cell, 70: 841-847, 1992; Resnick et al., Nature, 359: 550-551, 1992). The STO feeder cells were shown to produce a variety of growth factors (Robertson, 1987, supra; Matsui, 1992, supra; Schmitt et al., 1991, supra; Montesano et al., 1991, supra; Montesano et al., Cell, 66: 697-711, 1991; Hilton et al., J. Cell Physiol., 146: 207-215, 1991). Some of these were mediators of hepatocyte growth and function such as LIF and HGF (Montesano et al., (67) 1991, supra; Montesano, (66), 1991, supra; Hilton et al. 1991, supra). Hepatocytes were shown to express receptors for both LIF and HGF (Hilton, 1991, supra; Prat et al., Int. J. Cancer, 49: 323-328,

1991). LIF was reported to induce acute phase response proteins in hepatocytes (Baumann and Wong, J. Immunol., 143, 1163-1168, 1989), and HGF has been widely described as a potent hepatocyte mitogen (Zarnegar and Michalopoulos, Cancer Res., 49: 3314-3320, 1989; Strain et al., J. Clin. Invest,, 87: 1853-1857, 1991; Nakamura et al., Biochem. Biophys. Res. Commun., 122: 1450-1459, 1984). Both LIF and HGF stimulated (P>0.05) replication of PICM-19 cells when assayed in a 5% FBS and reduced STO feeder cell environment. Thus, two growth factors directly related to hepatocyte growth and function are present in the STO feeder layer and may support the development of hepatocytes from the primary epiblast culture.

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L17: Entry 18 of 22 File: USPT Jun 3, 1997

DOCUMENT-IDENTIFIER: US 5635609 A
TITLE: Particles prepared by transacylation reaction between an esterified polysaccharide and a polyamine, methods of preparation therefor and compositions containing same

Brief Summary Text (82):
Examples of proteins which may be used in the invention and which satisfy the conditions, which consist in being hydrophilic or else which may be treated in order to be hydrophilic, are albumins such as serum albumin, ovalbumin, alpha-lactalbumin, globulins, fibrinogen, casein, plant proteins such as soya or wheat proteins, glutenins which have preferably been degraded, solubilized scleroproteins, collagen, atelocollagen, gelatin, gelatin hydrolysates, peptones, hemoglobin, enzymes such as catalase, alkaline phosphatase, hormones, immunoglobulins or antibodies such as monoclonal antibodies.

Brief Summary Text (105):
Examples of living material which may be incorporated into the particles according to the invention are microorganisms for carrying out syntheses or bioconversions, such as bacteria, for instance those used for fermenting dairy products, or those used for water purification, or fungi such as mycorrhizas or yeasts such as, for example, the yeasts used in the manufacture of beer, or the yeasts used to give champagne its mousse, or microalgae, seeds to which various protective substances or substances influencing their germination or their growth have optionally been added, plant somatic embryos for producing synthetic seeds, plant apices, plant cells or tissues in particular for carrying out biosyntheses or bioconversions, living material from the animal kingdom, such as cells or tissues which may be used in particular to carry out toxicology tests in vitro, such as liver cells, chondrocytes, neurones, cells or groups of cells or tissues which may be used in the context of a cell therapy, such as the islets of Langerhans for treating diabetes, medullo-adrenal cells or chromaffin cells for treating Parkinson's disease or for treating chronic pains, or cells which may be used for the production of various biological substances such as hormones, enzymes, growth factors, interferon, clotting factors, or hybridomas for production of monoclonal antibodies, or cell constituents such as liver microsomes for carrying out bioconversions, or eggs, or gametes, embryos or genetic material from the animal kingdom or from the plant kingdom.

CLAIMS:

21. The particle of claim 19, wherein said living material is selected from the group consisting of a bacteria for fermentation of dairy products, a bacteria for water purification, a mycorrhiza, yeasts, yeasts for beer manufacture, yeasts for champagne manufacture, liver cells, chondrocytes, neurones, cells for therapy, islets of Langerhans for the treatment of diabetes, medullo-adrenal cells, chromaffin cells for the treatment of Parkinson's disease, chromaffin cells for the treatment of chronic pains, growth factors, interferon, coagulation factors, hybridomas for the production of monoclonal antibodies, gametes, and embryos.

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L17: Entry 17 of 22 File: USPT Nov 11, 1997

DOCUMENT-IDENTIFIER: US 5686239 A
TITLE: Hepatitis E virus peptides and methods

Detailed Description Text (139):
Cultures were incubated at 37.degree. C. in 5% CO.sub.2 for 3 hours to allow attachment and the medium was changed to a serum-free formulation and every 48 hrs thereafter. The serum-free formulation was a WME-based medium supplemented with growth factors, hormones, 10 mM HEPES (pH7.4), 100 ug/ml gentamicin, as has been described (Lanford, 1989).

Detailed Description Text (160):
The purified recombinant HEV peptides, 200 ng in 100 ul 0.05M sodium carbonate pH 9.5 (1.59 g Na.sub.2 CO.sub.3, 2.93 g NaHCO.sub.3, 0.02% sodium azide, pH 9.5, bring to 1000 ul), are pipetted into each well of a polystyrene microtitre plate. Plates are incubated at 37.degree. C. for 1 hour. After overnight incubation at 4.degree. C., the wells are washed in PBS-0.05% polyoxyethylene (20) monolaurate "Tween 20.TM." (Sigma) and blocked with 200 ul of 1% bovine serum albumin (BSA) in PBS for 1.5 hours at room temperature. The plates are rewashed with PBS-0.05% Tween 20.TM. and serum samples diluted 1:100 in antibody incubation buffer (10 mM Tris pH 7.5, 150 mM NaCl, 1% gelatin, 0.02% sodium azide) are added to incubate for 1 hour at room temperature. The wells are washed to remove any unbound 1st antibody and incubated for 1 hour at room temperature with 100 ul of 1 ug/ml of alkaline phosphatase conjugated goat anti-human IgG or IgM diluted in Antibody Diluent (1000 ml Tris buffered saline (40 mM Tris pH 7.5, 1M NaCl), 30 ml goat serum, 10 g bovine serum albumin, fraction V, 10 g non fat milk (Carnation), 1 g gelatin (EIA) grade, and 0.2 g thimersol (preservative), see Antibody Diluent Production, following). After final washing, 100 ul of alkaline phosphate substrate (Sigma) in diethanolamine buffer pH 9.8 (48.5 ml diethanolamine, dH.sub.2 O to 500 ml, 50 mg MgCl.sub.2, pH to 9.8, store in amber bottle) was added at room temperature for 30 minutes. The plates are read at an absorbance of 405 nm. A serum positive for anti-HEV antibodies will have an ELISA signal greater than 3-fold the signal generated with non-recombinant glutathione-S-transferase protein (pGEX fusion partner). The results are shown in Table 1.

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L9: Entry 8 of 10 File: USPT Jul 15, 1997

DOCUMENT-IDENTIFIER: US 5648253 A
TITLE: Inhibitor-resistant urokinase

Brief Summary Text (6):
To prevent systemic activation of plasminogen, the regulation of PA activity involves plasminogen activator inhibitors (PAIs). PAI-1 (originally designated endothelial type by Loskutoff and Edgington, J. Biol. Chem. 256: 4142-4145 (1981)), PAI-2 (originally designated placental type by Kawano, et al., Nature 217: 253-254 (1968)), and PAI-3 (originally designated urine type by Stump, et al., J. Biol. Chem. 261: 12759-12766 (1986)) are members of the serpin (serine protease inhibitor) superfamily. The inhibitors appear to function like other serine protease inhibitors, forming inactive covalent complexes with the target protease. PAI-1 rapidly inactivates both t-PA and u-PA. It is the major PAI of plasma, except during pregnancy. PAI-2 reacts more readily with u-PA than t-PA. PAI-2 is undetectable in the plasma of men and nonpregnant women, but rises to very high levels during late pregnancy.

Detailed Description Text (10):
The following abbreviations are used herein: bp, base pair(s); HRP, horseradish peroxidase; IU, international unit; mut-uPA, mutant synthetic u-PA; mut-uPA-DNA, mutant synthetic u-PA DNA; PA, plasminogen activator; PAI-1, epithelial-type plasminogen activator inhibitor; PAI-2, placental-type plasminogen activator inhibitor; PAGE, polyacrylamide gel electrophoresis; PBS, phosphate buffered saline, pH 7.4; scu-PA, single chain u-PA; SDS, sodium dodecyl sulfate; serpin, serine protease inhibitor; std-uPA, standard authentic u-PA; syn-uPA, synthetic u-PA; syn-uPA-DNA, synthetic u-PA DNA; tcu-PA, two chain u-PA; t-PA, tissue-type plasminogen activator; u-PA, urokinase-type plasminogen activator; WAP, whey acid protein.

Detailed Description Text (37):
Immunoblots were performed essentially as described by Towbin, et al., Proc. Natl. Acad. Sci. USA 76: 4350-4354 (1979) for u-PA as modified by Wagner and Binder, J. Biol. Chem. 261: 14,474-481 (1986). Apparent molecular weights (MW) were estimated by comparison with the relative migration of a prestained standard (BRL). Incubations with the primary antibody (goat anti-human u-PA IgG, American Diagnostica #398) were at 5 .mu.g/ml in PBS-GT (1X PBS pH 7.4, 3% w/v gelatin, 0.2% v/v Tween.TM.-20) for 12 to 24 h. Incubations with the secondary antibody (rabbit anti-goat IgG conjugated to alkaline phosphatase; Sigma A-2168) were at 1:1000 dilutions on the conjugate solution in PBS-GT for 4 to 8 h. The NBT-BCIP (BRL) color reaction was performed as recommended by the manufacturer. Membranes were stored in TE buffer, in the dark at 4.degree. C.

Detailed Description Text (74):
Immediately after injection embryos are transferred to recipient females, mature mice, such as CDI mice, mated to vasectomized male mice, such as CD mice. Recipient females are anesthetized using 2,2,2 tribromoethanol. Paralumbar incisions are made to expose the oviducts and the embryos are transferred into the ampullary region of the oviducts. The body wall is sutured and the skin closed with wound clips. Recipients are appropriately ear notched for identification and maintained until parturition.